

Complete Summary

GUIDELINE TITLE

Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck.

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Mackenzie RG, Hodson DI, Browman GP, Zuraw L. Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 13 p. (Practice guideline report; no. 5-6b). [22 references]

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SCOPE

DISEASE/CONDITION(S)

Newly diagnosed locally advanced (stage III and IV) squamous cell carcinoma of the head and neck (SCCHN)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
 Treatment

CLINICAL SPECIALTY

Internal Medicine
 Oncology
 Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To determine if hyperfractionated radiotherapy improves loco-regional control or survival compared with conventionally fractionated radiotherapy in patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radiotherapy with curative intent
- To evaluate the toxicity associated with hyperfractionation
- To address whether these regimens enhance the therapeutic ratio comparing benefits to toxicity

TARGET POPULATION

Adult patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radical radiotherapy with curative intent

INTERVENTIONS AND PRACTICES CONSIDERED

1. Hyperfractionated radiotherapy* protocols, such as small fractions of 1.0 to 1.2 Gy delivered twice daily (BID) or three times daily (TID)
2. Conventional radiotherapy
3. Concomitant chemotherapy

*Note: Hyperfractionated radiotherapy is considered, but not recommended as routine clinical practice.

MAJOR OUTCOMES CONSIDERED

- Survival (disease-free and overall)
- Loco-regional control
- Toxicity
- Therapeutic index (ratio of tumour control to treatment toxicity)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 to November 2000), CANCERLIT (1983 to September 2000) and the Cochrane Library (Issue 3, 2000) were searched with no language restrictions. "Head and neck neoplasms" (Medical Subject Heading [MeSH]) and "carcinoma, squamous cell" (MeSH) were combined with "fractionation" (MeSH), "dose

fractionation" (MeSH), "radiotherapy dosage" (MeSH) and "hyperfraction:" used as a text word. These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, randomized controlled trials. The citation lists of all retrieved articles were reviewed to identify additional trials. The proceedings of the 1999 and 2000 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new trials. On-going trials were identified through the Physician Data Query (PDQ) clinical trials database (U.S. National Cancer Institute).

2003 Update

The original literature search has been updated using MEDLINE (through January 2003), CANCERLIT (through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2001, 2002), and the American Society for Therapeutic Radiology and Oncology (2000-2002).

Inclusion criteria

The systematic review was limited to randomized trials and meta-analyses of randomized trials that compared hyperfractionated radiotherapy with a control arm using conventional radiotherapy (daily Monday to Friday). Three-arm trials investigating the addition of chemotherapy or radiosensitizers were included if there was a comparison of hyperfractionated radiotherapy versus conventional treatment and relevant and complete information could be extracted. Overall survival and loco-regional control were the primary outcomes of interest. Change in the therapeutic ratio comparing benefits to toxicity was also considered.

NUMBER OF SOURCE DOCUMENTS

7 randomized controlled trials (2 in abstract form) and 1 meta-analysis

2003 Update

2 meeting abstracts and one published report of a randomized controlled trial (RCT)

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Pooling of data was not attempted because of the small number of trials with complete information and the methodological problems inherent in several of the studies. Of the seven randomized controlled trials comparing hyperfractionation with conventional fractionation, two trials have been reported only in abstract form, two trials did not report whether or not prognostic factors were balanced between treatment groups and one trial included results for only the complete responders. In another trial, the total dose in the hyperfractionated radiotherapy arm was not higher than in the conventional radiotherapy arm. No data on overall survival were reported for one trial. Data on rates of acute and late toxicity were also not reported for this trial. Reports of two other trials did not include data on late complication rates. This left two studies which were fully published with mature follow-up, delivered an increase in total dose in the hyperfractionated radiotherapy arm compared with the conventional therapy arm, and reported data on survival, loco-regional control and acute and late adverse effects.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A draft report on altered fractionation in locally advanced squamous cell carcinoma of the head and neck (SCCHN) was submitted to the Head and Neck Cancer Disease Site Group (DSG). Subsequent feedback from DSG members suggested that there was too much information to be considered in a single guideline. Therefore, two guidelines were developed, one addressing hyperfractionated radiotherapy and the second addressing accelerated radiotherapy. It was suggested that both guidelines include a reference to the recently completed guideline on concomitant chemotherapy and radiation in the same group of patients.

Despite the publication of seven randomized controlled trials comparing hyperfractionated radiotherapy with conventional (daily fractionated) radiotherapy, the DSG expressed concern regarding the quality of the available data. Two of the studies had been published only as abstracts. Information reported by Sanchiz et al and Datta et al was incomplete with respect to the balance of prognostic factors. In addition, Sanchiz et al reported results only for complete responders. There was concern regarding the generalizability of the Brazilian study reported by Pinto et al. Ultimately, only two trials (European Organization for Research and Treatment of Cancer [EORTC] 22791 and Radiation Therapy Oncology Group [RTOG] 9003 provided convincing evidence of improved loco-regional control. The DSG noted that this benefit was not accompanied by improved disease-free or overall survival. A recent update of a third trial demonstrated significantly improved loco-regional control and survival with hyperfractionation, but the result have been reported only in abstract form. There was concern regarding the completeness of reporting of the incidence and severity

of late complications in all trials. The DSG members noted the paucity of data on salvage surgery in this group of patients. The group felt that it was premature to conclude that hyperfractionation with dose escalation does not increase late tissue complications.

In comparing the relative merits of hyperfractionation and accelerated fractionation in patients with locally advanced disease, the DSG members noted that there was evidence for improved loco-regional control for both strategies. However, the group rated modestly accelerated regimens somewhat higher because they could improve the therapeutic index without undue pressure on departmental resources. In general, fractionation regimens utilizing two or more fractions per day require more personnel, more machine time, and are more difficult to schedule than conventional daily fractionation. Hyperfractionation leads to a dramatic increase in the number of fractions. In all but one of the published hyperfractionation trials, the number of radiation treatments was doubled in the experimental arm. Because hyperfractionation is resource intensive, DSG members felt that the implementation of hyperfractionation would be difficult in Ontario, particularly in centres where a shortage of machine time contributes to waiting lists.

The DSG members concluded that current information does not support the use of hyperfractionated radiotherapy in adults with locally advanced squamous cell carcinoma of the head and neck at this time. Given the strength of the data supporting concomitant chemoradiation as summarized in the Cancer Care Ontario Practice Guideline Initiative (CCOPGI) practice guideline on concomitant chemotherapy and radiotherapy in SCCHN, the DSG members concluded that concomitant chemoradiation should be regarded as the treatment of first choice in patients with locally advanced SCCHN.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 112 practitioners in Ontario (15 medical oncologists, 25 radiation oncologists and 72 surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four

weeks (complete package mailed again). The results of the survey have been reviewed by the Head and Neck Cancer Disease Site Group.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- This group of patients should be considered for concomitant chemotherapy and conventional radiation as recommended in Cancer Care Ontario Practice Guidelines Initiative Guideline No. 5-6a titled "Concomitant Chemotherapy and Radiotherapy in Squamous Cell Head and Neck Cancer (Excluding Nasopharynx)" (see the [National Guideline Clearinghouse \[NGC\] summary](#)).
- Hyperfractionated radiotherapy cannot be recommended as routine clinical practice at this time.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Seven randomized controlled trials (two reported in abstract form) of hyperfractionated radiotherapy compared with conventional radiotherapy met the inclusion criteria. The results of a published meta-analysis of randomized controlled trials of hyperfractionated radiotherapy are also included in the original guideline document. In addition, limited evidence from two meeting abstracts and one published report (an additional randomized trial) have been included in the update.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

These guidelines may aid physicians in choosing an appropriate radiotherapy regimen for their patients with locally advanced squamous cell cancer of the head and neck.

POTENTIAL HARMS

- Hyperfractionated radiotherapy (multiple fractions per day) yields higher rates of acute toxicity compared with conventional radiotherapy (one fraction per day, five days per week).
- Data on the incidence and severity of late complications associated with hyperfractionation are incomplete. It is premature to conclude that

hyperfractionation with dose escalation does not increase late tissue complications.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Although the improvements in loco-regional control and survival are promising, longer follow-up and more complete information on late complications will be needed to meaningfully compare these results to those achieved with concomitant chemoradiation in locally advanced squamous cell carcinoma of the head and neck.
- Conclusions regarding loco-regional control are limited by the quality of the published data. To date, only three of seven randomized controlled trials have provided convincing evidence of improved loco-regional control with hyperfractionation compared with conventional radiotherapy. In one of these three studies, improved loco-regional control was accompanied by an increase in overall survival. Two other randomized controlled trials have documented improved overall survival with hyperfractionation, but both studies have been criticized for failing to report complete data.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Mackenzie RG, Hodson DI, Browman GP, Zuraw L. Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Jan [online update]. 13 p. (Practice guideline report; no. 5-6b). [22 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Nov 27 (revised online 2003 Jan)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health Long-Term Care

GUIDELINE COMMITTEE

Provincial Head and Neck Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Head and Neck Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

The following companion guidelines are also available:

- Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx). Toronto (ON): Cancer Care Ontario (CCO); 2000 Mar [online update]. Various p. (Practice guideline; no. 5-6a); (see the [National Guideline Clearinghouse \[NGC\] summary](#)).
- Accelerated radiotherapy for locally advanced squamous cell carcinoma of the head and neck. Toronto (ON): Cancer Care Ontario (CCO); 2000 Nov. Various p. (Practice guideline; no. 5-6c).

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2002. The information was verified by the guideline developer as of July 8, 2002. This summary was updated by ECRI on June 23, 2003. The updated information was verified by the guideline developer on July 16, 2003.

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